



Review

Marketing dietary supplements in the United States: A review of the requirements for new dietary ingredients

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Abstract

Since the passage of the Dietary Supplement Health and Education Act in 1994, the marketplace for dietary supplements has experienced dramatic growth. New products have redefined the entire marketplace, and new ingredients are introduced to consumers at lightning speed. As part of this act, laws were passed to ensure the safety of new dietary ingredients introduced into the United States marketplace. But more than 11 years later, these laws are frequently misunderstood, and more frequently ignored. This article reviews the regulatory landscape of new dietary ingredients and defines the issues manufacturers must contend with to legally market dietary supplements with new dietary ingredients in the U.S.

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1. Introduction

On October 15 of 1994, the dietary supplement health and education act (DSHEA) was passed by Congress, ushering in a new regulatory scheme for dietary supplements. Little could anyone have known on that day what economic impact DSHEA would have on the entire category. New products were introduced at lightning speed,

packed with novel new dietary ingredients and a myriad of “structure and function” claims authorized under the new law. The American public was re-introduced to an alternative form of healthcare that emphasized prevention and wellness. Since the passage of DSHEA, the dietary supplement marketplace has grown categorically with new products finding their way into all U.S. retail channels.

As part of the passage of DSHEA, a new law requiring pre-market safety notification for new dietary ingredients (NDI) became part of the new regulatory landscape. The concept of this pre-market review is easily under-

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stood: every dietary ingredient in the market before October 15, 1994 is considered an old dietary ingredient and presumed to be safe; every ingredient (with some exceptions) marketed after October 15, 1994 is a new dietary ingredient requiring Food and Drug Administration (FDA) pre-market review of safety. Based on this definition, one has simply to determine if an ingredient to be marketed was included in a product marketed before October 15, 1994. However, while the concept seems easy to understand, in practice, it has not been so easy to follow. After more than 11 years, there is little industry comprehension of this section of DSHEA.¹ Although NDI notification is a legal requirement, many marketers are much less aware of the requirements than they are concerned about their implications. However, this legal requirement is not likely to be ignored by FDA. Understanding the legal distinction between “old” and “new” dietary ingredients is imperative for any company marketing a dietary supplement product in the U.S. marketplace.

2. Old dietary ingredients

Given the history and legend of many dietary ingredients, it is easy to presume that most dietary ingredients are old. The intent by FDA in defining ingredients as old (or “grandfathered”) was to establish that these ingredients had already been in the food supply and thus presented no harm to the public. Through a history of use in the U.S. marketplace, and unless evidence suggested otherwise, the ingredient has proven itself safe and rightly classified under “old” status. Since the October 15, 1994, enactment of DSHEA, there was little discussion on the definition of an “old” dietary ingredient with the exception of some FDA informal guidance; however, in 2004, the agency sent warning letters to 23 manufacturers of the ingredient androstenedione (andro), which established an FDA regulatory position on the legal definition of “old” dietary ingredients.² FDA stated in the warning letters that andro did not qualify for “grandfathered” status under DSHEA because there was no reliable evidence that andro was “lawfully” marketed as a dietary ingredient prior to October 15, 1994. Although the word “lawfully” had previously been men-

tioned by FDA in other NDI correspondence,³ in this case, FDA invoked its statutory authority under DSHEA to remove dietary supplement products containing andro from the marketplace by applying the new/old dietary ingredient legal requirements. FDA stated that the mere presence of the ingredient andro in the marketplace prior to October 15, 1994, was not sufficient to legally establish it as an “old” dietary ingredient, but rather it must have been lawfully marketed during such time. According to FDA, a “lawfully” marketed dietary supplement requires that a manufacturer or distributor have written evidence that the ingredient in question is chemically identical to a dietary ingredient that was legally marketed in the U.S. before October 15, 1994.⁴ For those ingredients that qualify as “lawfully” marketed, FDA considers independent documentation proving that an ingredient is old to be a product invoice, bill of lading, product label or labeling, or a catalogue with a date showing evidence of marketing before October 15, 1994.⁵

FDA has also made the distinction that “market as” is not the same as “sold as”. In March of 2001 in the case of *Pharmanex v. Shalala*,⁶ the government successfully argued that the mere presence of an ingredient in food is not sufficient evidence to prove prior marketing of the ingredient in that food. The ingredient in question must have been marketed for its own properties, not that of the food which contained the ingredient.

3. New dietary ingredients

Section 8 of DSHEA defines a new dietary ingredient as “a dietary ingredient that was not marketed in the United States before October 15, 1994.”⁷ If a dietary supplement contains a “new dietary ingredient,” then a manufacturer or marketer of that product is legally required to notify FDA 75 days prior to the introduc-

¹ See Section 413(c) of the Food, Drug and Cosmetic Act (“FDA Act”).

² See FDA, Center for Food Safety & Applied Nutrition (CFSAN), Androstenedione Warning Letters, available at <http://www.cfsan.fda.gov/~dms/andrlist.html#letter>.

³ Letter from Linda S. Kahl, Ph.D., Acting Director, Division of Programs & Enforcement Policy, Office of Special Nutritional, CFSAN to W. Patrick Noonan, Sunrider Corporation (August 16, 1995) available at <http://www.fda.gov/ohrms/dockets/dockets/95s0316/m000002.pdf>.

⁴ Letter from Felicia B. Satchell, Office of Nutritional Products, Labeling and Dietary Supplements to Holly M. Bayne, Hyman, Phelps and McNamara, P.C., regarding new dietary ingredient notification for Glucose Metabolism Modulator, July 15, 2001.

⁵ U.S. Food and Drug Administration Import Alert #45-06, Automatic detention of Stevia leaves, extract of Stevia leaves, extract of Stevia leaves and food containing Stevia. Revised February 2, 1996, Attachment revised May 28, 2003. Available at http://www.fda.gov/ora/fiars/ora_import_ia4506.html.

⁶ *Pharmanex Inc. v. Shalala*, Case No. 2: 97CV262K, CD. Utah, March 30, 2001.

⁷ See Section 413(c) of the Food, Drug and Cosmetic Act (FDC Act).

tion of the ingredient into the market with sufficient data to provide substantiation on the ingredient's general safety.⁸ This section of DSHEA established a mechanism for FDA to ensure the safety of ingredients in dietary supplement products. By assuring the "general safety" of new dietary ingredients, the public could be assured of the safety of these ingredients in marketed dietary supplement products. The FDC Act states that a dietary supplement containing an NDI shall be deemed adulterated unless it meets one of the following requirements⁹: (1) it is a dietary supplement that contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered and (2) there is a history of use or other evidence of safety establishing that the dietary ingredient will *reasonably* be expected to be safe. The manufacturer must provide FDA at least 75 days in advance with information qualifying the safety of the new dietary ingredient. Emphasis is added to the word "reasonably" because it is precisely this interpretation of the FDC Act that has caused such confusion among manufacturers, marketers and distributors.

Based on a review of the NDI submissions to date, reasonable data to support safety is a more significant term than manufacturers or marketers understand. Of the 280 plus NDI submissions presented to FDA for new dietary ingredients, less than 30% have been accepted by FDA as showing an adequate basis for safety. Most have been rejected on the grounds that the data presented to establish safety are not adequate. FDA expects to see NDI filings that contain scientific evidence to support the safety of the ingredient as an ingredient used for food purposes or as an article of food. For this reason, evidence demonstrating use of a dietary ingredient for therapeutic purposes (e.g. cancer treatment) would not qualify that ingredient as safe for food use.

There are six procedural requirements that must be followed when filing an NDI submission: (1) name and address of manufacturer or distributor of the new dietary ingredient; (2) name of the NDI; (3) description of the NDI including a full characterization of the ingredient; (4) level of NDI in dietary supplements which would include the amount included in dosage form products and expected daily consumption; (5) conditions of use recommended in product labeling which includes the labeled suggested population for the ingredient; and

most importantly; (6) evidence proving the ingredient is safe. Despite the availability of past NDI submissions as a guide for manufacturers or distributors to understand FDA expectations in filings, many of these requirements are not followed during submissions. In those cases in which the NDI filings do not follow these legal requirements, FDA will reject the filing as incomplete. The process for filing NDIs should be followed as diligently as the creation of a new formula for market. Errors and omissions can set back an NDI filing 6–9 months. Omitting details such as failing to provide full text excerpts of all scientific data used to support the safety of the ingredient, translated into English, should not happen to those serious about receiving accepted NDI status.

Other more complicated legal issues do arise during the process. These merit further explanation:

- (1) Race to market provision—The presence of an FDA-approved investigational new drug (IND) application plus a published clinical study that occurred before marketing of NDI: the FDC Act definition of a dietary supplement, as a matter of law, excludes any dietary ingredient that was approved as a new drug¹⁰ or an article authorized for investigation as a new drug, antibiotic or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval or authorization, marketed as a dietary supplement or food.¹¹ If a pharmaceutical or other company receives FDA approval for an IND application for which the clinical studies were later published before the NDI was marketed, then the dietary ingredient is disqualified as a dietary supplement under DSHEA and further marketing is unlawful. There are some examples of this issue in past submissions of NDIs to FDA. FDA also asserts that it is not relevant in this determination if the IND is currently in force, only that it was filed and accepted by FDA at some time prior to the marketing of the NDI. A thorough pre-market review is required prior to preparing the submission of an NDI, and in such review, it is important to determine the scope of previous IND investigations. It is the presence of a single study, published in scientific literature that may disqualify an ingredient from definition as a dietary supplement.

⁸ See Section 413(a)(2) of the FDC Act.

⁹ See Section 402(f) of the FDA Act.

¹⁰ See Section 505 of the FDC Act.

¹¹ See Section 201(ff)(3)(A)(B) of the FDC Act.

- (2) Ingredient represented in NDI submission does not meet the legal definition of a dietary supplement. The legal definition of a dietary ingredient¹² includes: (1) a vitamin; (2) a mineral; (3) a herb or other botanical; (4) an amino acid; (5) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (6) a concentrate, metabolite, constituent, extract or combination of any ingredient described above. There has been some debate about the interpretation of this legal definition, which will continue into the future as FDA and the dietary supplement industry attempt to reach compromise on which ingredients qualify under this definition and which do not. In a warning letter issued to Blue Light Inc. in 2000,¹³ FDA defined “dietary substance” under a common-sense understanding of the term, to mean simply substances customarily used as human food or drink.” Examples of ingredients that FDA has rejected as not meeting the definition of a dietary supplement include some extracts from trees, some amino acid derivatives, hormones and synthetic substances.
- (3) Reference to Chinese herbal medicine as a basis for safety is not sufficient: many dietary ingredients include great historical precedent for their safety of use as a dietary supplement. However, unless one can clearly demonstrate that the ingredient that appears in Chinese herbal medicine is identical to the ingredient included in an NDI submission, and, that the ingredient has been used at a dosage that is consistent with the dosage recommendations made in the NDI submission, the references used are insufficient. Many references present pharmacological, clinical or toxicological information on the source ingredient in a form or dosage that is different from the ingredient or dosage included in the NDI submission. If the evidence does not present the dietary ingredient as being safe when consumed as a component of food, then the information should be omitted from the submission. Non-pertinent data have been shown to negatively affect FDA evaluation on the safety on an ingredient. Further, information should not be submitted merely because it exists. One well-characterized study is superior to 20 studies where the ingredient cannot be adequately characterized as identical to the ingredient included in an NDI submission.

There are certainly other requirements of the NDI process that deserve attention, and a review of the publicly available past NDI submissions can provide some valuable insight into the process.¹⁴ In addition, FDA has taken notice of the confusion surrounding the NDI process.

On October 20, 2004, FDA published a guidance document entitled “Regulatory Strategy for the Further Implementation and Enforcement of the Dietary Supplement Health and Education Act of 1994”¹⁵ in which they announced three steps to ensure that dietary supplements that contain NDIs are not adulterated. The first step was to convene a public meeting to obtain comment on issues pertaining to NDIs. The second step was an announcement of FDA’s intent to bring enforcement actions against marketed dietary supplements that contain NDIs for which a required 75-day notification has not been submitted. The third step involved FDA plans to bring further enforcement actions against marketed dietary supplements that are adulterated because they contain an NDI for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. These regulatory steps are an effort to ensure compliance with the requirements of DSHEA for NDIs and inform those who have ignored the requirements that they do so at their own legal risk. Pending are FDA responses to questions pertaining to the NDI submission process, to be published in the Federal Register in 2006. This may help clarify some of the ambiguity that currently exists. FDA’s guidance document of 2004 is clearly intended to reinforce that the requirements for marketing new dietary ingredients must be followed and despite the apparent difficulty in compliance, FDA expects any manufacturer or distributor to comply with these laws.

4. Conclusion

The dietary supplement industry can be defined by its new products. Manufacturers are either introducing new products or reinventing old ones. To the U.S. consumer, it would appear that there is a dietary supplement for every health ailment in existence. Products for joint health, cognitive function, vision, skin, heart—a product or ingredient for any condition of the human body that could require nutritional support. The continuity of

¹² See Section 201(ff)(1) of the FDC Act.

¹³ FDA, Department of Health & Human Services, Warning Letter to Blue Light Inc., Ithaca, NY. December 18, 2000.

¹⁴ Available at <http://www.fda.gov/>.

¹⁵ CFSAN, Office of Nutritional Products, Labeling and Dietary Supplements, November 2004.

new products is also an indication of a highly dynamic industry, where entrepreneurialism still exists and highly creative marketers are fortunate enough to work on products through the entire product lifecycle.

It is also an industry with regulations designed to protect U.S. consumers against unsafe ingredients and potential harm. To the haphazard, overly ambitious marketer, these regulations are often overlooked. For those serious about complying with the legal requirements for new dietary ingredients, the act of compliance can be a difficult task as companies struggle to comprehend laws that seem to evolve over time. Despite these dif-

ficulties, these regulations are not optional and FDA expects all who wish to participate in this entrepreneurial arena to follow their laws. In the near future, FDA will begin to act on its pledge to remove products it deems “unsafe” from the market and force other products (with new ingredients) to undergo review as part of the new dietary ingredient submission process. For those companies interested in long term success, careful and diligent research into the legal status of every dietary ingredient included in a dietary supplement should be an essential part of any new product development effort.